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Tumor volume dynamics and tumor growth rate in *ALK*-rearranged advanced non-small-cell lung cancer treated with crizotinib

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ABSTRACT

Purpose: The purpose of the study is to investigate volumetric tumor burden dynamics and tumor growth rates in *ALK*-rearranged advanced NSCLC patients during crizotinib monotherapy.

Methods: The study included 44 *ALK*-rearranged advanced NSCLC patients treated with crizotinib monotherapy as their initial ALK-directed therapy, who had at least one measurable lung lesion and at least two follow-up CT scans, and experienced tumor volume increase while on crizotinib. The tumor volume (in mm^3) of the dominant lung lesion was measured on serial CT scans during therapy for analysis of tumor growth rates after the volume nadir.

Results: A total of 231 volume measurements from the nadir to the end of crizotinib therapy or the last follow-up in 44 patients were analyzed in a linear mixed-effects model, fitting time (in months since baseline) as a random effect. When measured from the volume nadir, the tumor growth rate of the logarithm of tumor volume ($\log_e V$) was 0.04/month (SE = 0.012, P = 0.0011) in the unadjusted model. When adjusted for the baseline volume ($\log_e V_0$), the growth rate was again 0.04/month (SE = 0.011, P = 0.0004). When adjusted for clinical variables and $\log_e V_0$, the growth rate was 0.045/month (SE = 0.012, P = 0.0002), indicating that the tumor growth rate after nadir in this cohort remains very close to 0.04/month regardless of $\log_e V_0$ or clinical factors.

Conclusions: Tumor volume growth rate after nadir in *ALK*-rearranged NSCLC patients treated with crizotinib was obtained, providing objective reference values that can inform physicians when deciding to keep their patients on ALK directed therapy with slowly progressing lung cancer.

1. Introduction

Precision therapy for lung cancer is based on the identification of oncogenic drivers specific to a subgroup of patients, who benefit from agents that target these drivers [1–3]. Identification of epidermal growth factor receptor (*EGFR*) mutations in non-small-cell lung cancer (NSCLC) patients who benefit from EGFR inhibitors and the identification of anaplastic lymphoma kinase (*ALK*) rearrangements in NSCLC that respond very well to ALK inhibitors are the two representative examples of clinical application of precision therapy approaches to lung cancer [4–8]. Five ALK-directed agents are currently available by prescription, including crizotinib, alectinib, ceritinib, brigatinib and lorlatinib [9]. Among them, crizotinib received an initial FDA approval in 2011 and has been used as a major treatment option for *ALK*-rearranged NSCLC, with the overall response rates of 65–74 %, median progression-free survival (PFS) of 7.7–10.9 months, and median overall survival (OS) of 20.3–45.8 month or longer [8,10–13].

However, a major challenge of precision therapy is eventual tumor progression due to acquired resistance, which occurs in virtually all patients with an initial response [3,12]. In these patients, tumors tend to grow back slowly over time after reaching the nadir (the smallest tumor burden since baseline), indicating some tumor cells remain sensitive to therapy [14–18]. In these clinical scenarios, targeted therapy is often continued beyond RECIST progression, because these patients tend to be symptom-free with slowly growing tumors. An important limitation of RECIST is a lack of definition of slow tumor growth, which is a common clinical scenario in patients with specific oncogenic driver mutations treated with targeted therapy [1,14–19].

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In the trials of crizotinib for *ALK*-rearranged NSCLC, patients who experienced RECIST progression were allowed to continue crizotinib if they are judged by investigators to still be receiving clinical benefit [10]. In a phase 3 trial of crizotinib in *ALK*-rearranged NSCLC patients, 33.5 % (58/173) of patients continued crizotinib beyond RECIST progression, with a median duration of treatment beyond progression being 15.9 weeks (range, 2.9–73.4 weeks) [10]. These results demonstrate that one-third of patients treated with crizotinib continued to derive clinical benefit for months or sometimes years beyond RECIST progression. The observation emphasizes the importance of objective tools to define slow tumor progression in patients after an initial tumor response that can effectively guide treatment options beyond RECIST progression. Such a tool is particularly important to guide for clinicians as to when to continue treatment beyond progression, and also when to consider switching therapy, given the availability of newer ALK inhibitors that are effective in treating tumors with acquired resistance to crizotinib [20–24].

Prior studies by our group and others have used tumor volume analyses to characterize tumor response and progression of NSCLC patients treated with EGFR and ALK inhibitors [25–29]. Tumor volume can capture three-dimensional tumor burden from CT data, has been shown to be more reproducible than RECIST-based size measurements, and thus can accurately characterize smaller tumor burden changes than RECIST [30–33]. Based on these advantages, volumetric tumor growth rate after nadir has been characterized in *EGFR*-mutant advanced NSCLC patients treated with EGFR inhibitors and provided a reference value of 0.12/month for the logarithm of the volume ($\log_e V$) as an overall tumor growth rate in these patients [26,28,34]. This approach, established in *EGFR*-mutant patients, can be applied to other cohorts of patients treated with effective targeted therapy to evaluate their specific quantitative characteristics of tumor growth.

The purpose of the present study is to analyze the tumor volume growth rates in *ALK*-rearranged advanced NSCLC patients after reaching a volume nadir during crizotinib treatment as their first ALK-directed therapy, in order to objectively characterize tumor volume dynamics and develop guidelines for therapeutic decisions.

2. Materials and methods

2.1. Patients

Forty-four patients with advanced *ALK*-rearranged NSCLC treated with crizotinib monotherapy as their initial ALK-directed therapy at our institution between November 2008 and June 2016 were included. All patients had at least one measurable lung lesion (≥10 mm in the longest diameter) on baseline chest CT and at least two follow-up CT scans during crizotinib therapy, and experienced tumor growth assessed volumetrically while on crizotinib [26,30,35]. CT scans and medical records of these patients were retrospectively reviewed following the institutional review board approval as done in the past [26,28,30,36].

Demographics and clinical characteristics of the patients, including age, gender, race, smoking history, tumor histology, stage at diagnosis, and the treatment line of crizotinib therapy were collected from the medical records [27]. All patients had advanced NSCLC at the time of initiation of crizotinib therapy, including 37 patients with stage IV disease at diagnosis and 7 patients who experienced disease recurrence after an initial diagnosis of stage I-III NSCLC.

2.2. CT tumor volume measurement and analysis

The baseline and follow-up chest CT scans were performed to evaluate response to crizotinib as a part of their clinical care. A thoracic radiologist (T.H.) performed the tumor volume measurements of dominant lung lesions (one lesion per patient) on the baseline CT and on all follow-up CT scans during crizotinib therapy, using a previously validated technique on the volume analysis workstation (Vitrea 7.3.0.322; Vital Images, Minnetonka, MN) [25,26,28,30]. In patients with more than one measurable lung lesion, the largest lung lesion was selected as a dominant lesion based on the longest diameter of the lesion, as before [25–28,30].

Previous studies have described the workflow for tumor volume measurements for advanced NSCLC with *EGFR* mutations treated with EGFR-directed therapy [25,26,28,30,36]. In brief, axial chest CT images were loaded and displayed on the workstation equipped with tumor volume segmentation software. The reader manually selected the dominant lung lesion by a mouse click to automatically segment the lesion from the surrounding structures using a three-dimensional seed-growing algorithm. Then, the reader visually assessed the boundary of the segmented lesion for manual adjustment of the boundary as needed. After segmentation and manual correction, tumor volume was automatically calculated by the software [25,26,28,30,36]. The intra- and interobserver variability of tumor volume measurements using this technique in advanced NSCLC patients has previously demonstrated a high reproducibility with interobserver concordance correlation coefficients (CCC) of 0.990 [30].

2.3. Statistical analysis

A total of 231 volume measurements (median: 3.5, range: 2–21) from nadir to the end of crizotinib therapy or to the last follow-up in 44 patients were analyzed. As described previously, a linear mixed effects model, fitting time as a random effect [37], was fitted to the repeated measures of volume data to estimate the effect of time and other prognostic factors on tumor growth [26,28]. The tumor volume, originally obtained in mm^3, was transformed to the natural logarithm scale ($\log_e V$) [26,28,34]. The first model was built adjusting only for time in months from baseline. In the second model, the baseline volume ($\log_e V_0$; the tumor volume measured on the baseline scan performed before the initiation of TKI therapy) was added as it may influence the tumor volume and its growth rate. In the third model, $\log_e V_0$ and clinical characteristics were added, to determine if clinical variables have significant effect on the tumor growth [26,28].

3. Results

Demographics and clinical characteristics of patients are summarized in Table 1. The median time on crizotinib monotherapy was 14.9 months. The median time from baseline to tumor volume nadir was 4.4 months. The median baseline volume was 14,860 mm^3 (range: 835–484,222 mm^3), the median nadir volume was 4244 mm^3 (range: 7–146,463 mm^3), and the median percent volume change at nadir compared to baseline was −74.4 % (range: −99.6 to −15.9 %). The volumetric tumor growth of 44 patients from nadir to termination of crizotinib therapy or the last follow-up scan is shown in Fig. 1. A linear mixed effects model was fitted to predict growth of $\log_e V$, adjusting for time from baseline.

In the first model which estimated $\log_e V$ as a function of time in month from baseline, the following formula was obtained:

$$\log_e V = 0.04 * \text{time} + 7.86.$$

In this formula, the regression coefficient for time, 0.04/month, represents the volumetric tumor growth rate of $\log_e V$ (SE = 0.012, 95 % CI: 0.016-0.063, P = 0.0011).

The second model after adjusting for $\log_e V_0$ as a fixed effect estimated $\log_e V$ as follows:

$$\log_e V = 0.04 * \text{time} + 1.03 * \log_e V_0 - 2.09$$

Baseline volume ($\log_e V_0$) was a significant predictor of $\log_e V$ ($P < 0.001$), with the coefficient of 1.03. The growth rate of $\log_e V$, obtained as a regression coefficient for time, was also 0.04/month (SE = 0.011, 95 % CI: 0.018–0.063, P = 0.0004) after adjusting for $\log_e V_0$,

Table 1
Clinical characteristics of the patients.

Clinical Characteristic	Number of patients
Age	
Median [range]	56 years [29–91]
Sex	
Male	17 (39 %)
Female	27 (61 %)
Race	
White	36 (82 %)
Asian	3 (7 %)
Black	3 (7 %)
Hispanic	1 (2 %)
Other	1 (2 %)
Smoking Status	
Never	29 (66 %)
Former	11 (25 %)
Current	4 (9 %)
Stage IV	
No	7 (16 %)
Yes	37 (84 %)
Line of Therapy	
1	19 (43 %)
2	14 (32 %)
3	6 (14 %)
4	4 (9 %)
5	1 (2 %)

indicating that the tumor growth rate is 0.04/months in this cohort irrespective of the baseline volume.

The third model adjusted for stage at diagnosis (stage IV vs. others) and smoking status (current/former vs. never smoker) in addition to $\log_e V_0$, and provided the following formula:$\log_e V = 0.045 * time + 1.00 * \log_e V_0 + 0.36 * stage - 0.06 * smoking - 2.11$Time was again statistically significant as a predictor of $\log_e V$ in this model as well, with an estimate of the regression coefficient of 0.045 (SE = 0.012, 95 % CI: 0.022–0.069, P = 0.0002) after adjusting for these variables, similar to 0.04/month obtained in the first two models. The baseline volume ($\log_e V_0$) was also a significant predictor of $\log_e V$ (P < 0.001), whereas stage (P = 0.5824) and smoking status (P = 0.8996) were not. These two clinical variables, though not significant as predictors for $\log_e V$ in this cohort, were chosen in the third model based on the prior studies of tumor growth model during precision lung cancer therapy [26,28] to test if inclusion of these clinical factors affects the tumor growth rate. Other clinical variables from Table 1 were not significant predictors for $\log_e V$, either.

Representative cases of slow tumor growth with reference to the tumor growth rate obtained in the above models are shown in Figs. 2 and 3, with a rate of 0.02/month for $\log_e V$ for both cases.

4. Discussion

The present study provides the tumor volume growth rate after nadir in *ALK*-rearranged NSCLC patients treated with crizotinib as their initial ALK-directed therapy, which can be a reference value of the rate of tumor volume growth in patients progressing on crizotinib. Though ALK inhibitors have been widely used in advanced NSCLC patients with *ALK* rearrangements and a third of patients continue therapy with crizotinib beyond progression, objective assessments and guidance on continuing the ALK inhibitor therapy in these patients beyond progression has been limited. The results of the present study serve as the initial observation that can be further validated in additional cohorts of crizotinib-treated patients, and can also be a reference to address the rate of tumor progression in patients treated with newer ALK-directed agents with longer treatment durations than crizotinib.

Conventional evaluation of tumor progression using RECIST has a number of limitations, and emerging issues are noted specifically for patients undergoing precision cancer therapy [15]. One of these issues is that RECIST simply relies on the percent change of tumor burden in comparison with the prior time point (the baseline to define response or the nadir to define progression), and does not incorporate the tumor burden dynamics over time, or tumor growth rate, in characterizing tumor progression during therapy [28,38,39]. The current management plans as stated in therapeutic protocols of targeted agents for patients with oncogenic driver mutations is that patients can be treated beyond progression at the discretion of the investigators. This has been a vague management guide and provides challenges for practitioners who are not experienced with the agents enough to make appropriate decisions for their patients.

Effective precision therapy for patients with lung cancer harboring targetable oncogenic drivers has been shown to demonstrate a characteristic pattern of tumor burden dynamics during treatment period, noted as an initial marked decrease of tumor burden during the first 2–6 months followed by a period of gradual tumor regrowth after nadir due to acquired resistance [25–28,34]. Given this characteristic pattern noted in different cohorts of oncogenic driver mutations treated with effective targeting agents, objective assessment of tumor growth rate

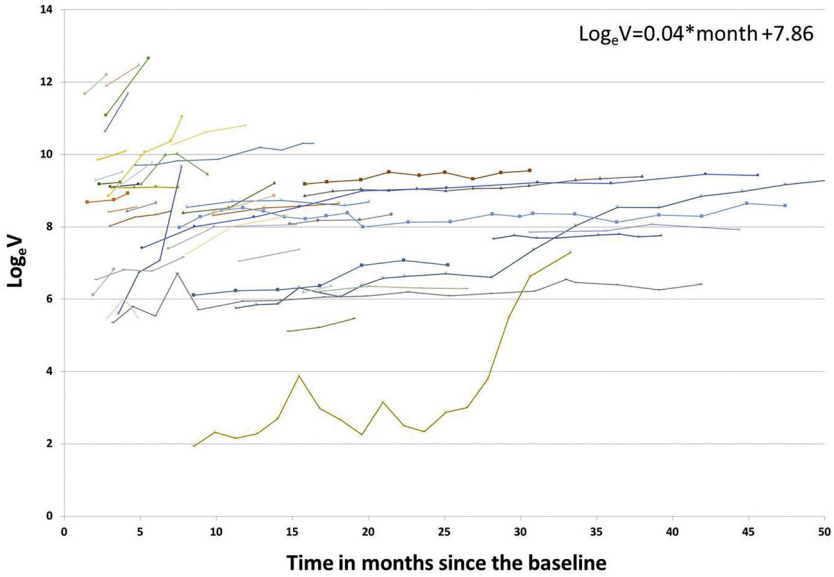

Fig. 1. Spider plot represents the volumetric tumor growth of 44 patients from their nadir during crizotinib therapy.

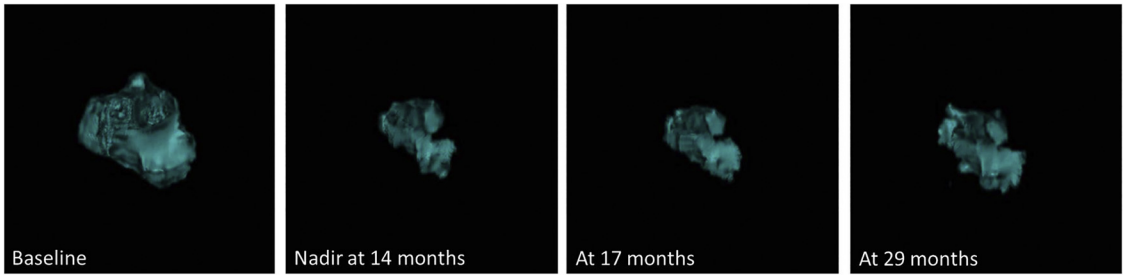

Fig. 2. A 29 year-old man with stage IV adenocarcinoma treated with crizotinib as the first-line therapy as the representative case of slow tumor growth.
The tumor at baseline measured 31,958 mm^3. The tumor responded to crizotinib and reached its volume nadir when it measured 9697 mm^3 at 14 months of therapy. The tumor started to gradually increase after the nadir, measuring 10,337 mm^3 at 17 months and 13,356 mm^3 at 29 months. Overall growth rate after the nadir was 0.02/month for log_eV during crizotinib therapy, indicating a slow tumor growth.

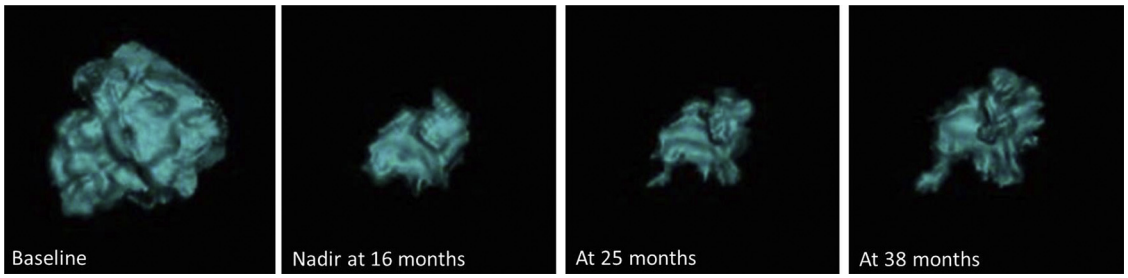

Fig. 3. A 71 year-old woman with stage IV adenocarcinoma treated with crizotinib as the forth-line therapy, representing a slow tumor growth after nadir.
The tumor at baseline measured 17,796 mm^3. After response to crizotinib, the tumor reached its volume nadir at 16 months of therapy, measuring 6975 mm^3. The tumor volume gradually increased after the nadir, measuring 8037 mm^3 at 25 months, and 11,998 mm^3 at 38 months. Overall growth rate after the nadir was 0.02/month for log_eV during crizotinib therapy, representing a slow tumor growth.

from serial CT scans during therapy will help to guide therapeutic decisions beyond RECIST progression in these patients. This approach may also provide insights to understand the biological behavior of tumors among subgroups of patients with specific oncogenic drivers.

This study followed the strategy of tumor volume measurements and tumor volume growth rate analysis that has been established in the prior studies of *EGFR*-mutant advanced NSCLC patients treated with EGFR inhibitors [25,26,28]. Use of the validated tumor volume segmentation and measurement technique is advantageous, because of high reproducibility of the technique which is equipped on a commercially available volume analysis workstation [30]. This technique has been successfully used to define volumetric parameters associated with prolonged survival in advanced NSCLC patients with *EGFR* mutations treated with EGFR inhibitors and in patients with *ALK* rearrangements treated with crizotinib [25–28,30]. The method of tumor growth rate analysis was developed after a careful review of literature on the topic of tumor growth assessments, utilizing transformation of tumor volume originally measured in mm^3 into the natural logarithm scale (log_eV), which was assessed in a linear mixed effects model fitting time as a random effect [28]. This method successfully characterized tumor volume growth after nadir in *EGFR*-mutant patients during EGFR-inhibitor therapy, and provided a reference value of the growth rate after the nadir which was shown to be 0.12/month for log_eV in two independent cohorts [26,28]. Building on these prior efforts, the present study reports an initial step of the application of the approach to *ALK*-rearranged NSCLC patients treated with crizotinib, as a representative cohort treated with the agent as a standard care since 2011.

Although similar patterns and characteristics are noted in tumor volume kinetics after nadir between the EGFR inhibitor-treated cohorts and the ALK inhibitor-treated cohort, the actual values of tumor growth rate for log_eV are different between the ALK cohort in the present study and the previously published EGFR cohorts [26,28]. This is somewhat expected as these tumors are harboring different oncogenic driver mutations treated with different agents. Interestingly, the overall tumor growth rate after nadir in ALK inhibitor-treated cohort (0.04/month for log_eV) was much slower compared to 0.12/month in the EGFR inhibitor-treated cohorts in the prior studies [26,28]. The results can be partly explained by the observation made in an updated analysis of a phase 3 trial of first-line crizotinib, which reported the duration of crizotinib treatment ranging from 0.4 to 63.5 months (median: 14.7 months), indicating that some patients stay on crizotinib for a long period of time which can be 5 years or longer [13]. On the other hand, EGFR cohorts demonstrate remarkably similar PFS curves in multiple studies, with most patients coming off from therapy around 18–24 month [40]. The different growth rates between EGFR and ALK cohorts also indicate that the tumor growth rates after nadir is specific to oncogenic driver mutations and targeting agents, and thus the quantitative characterization of this feature needs to be done in each driver mutation cohort and each agent.

The slower growth rate in the ALK cohort can also be partly due to the availability of other ALK-directed agents for *ALK*-rearranged patients. The present cohort of patients was treated between 2008 and 2016 when newer ALK inhibitors were becoming available, first in the clinical trial settings and then in the standard care setting, following the approval of ceritinib in 2014 and alectinib in 2015 for patients who progressed on crizotinib. The tumor growth rate obtained in the present cohort can still be considered as a reference value for the rate of tumor growth of patients who are receiving benefits from crizotinib in the clinical setting, because the decisions as to continue crizotinib or switch to different ALK-directed therapy were based on the overall clinical judgement of the treating physicians.

Although the actual values of tumor growth rate were different between the present *ALK*-rearranged cohort and the previously published *EGFR*-mutant cohorts, the rate was not affected by different models adjusting for the baseline volume or clinical variables in either of the cohorts. Tumor growth rate remained close to 0.04/months in the present cohort of *ALK*-rearranged patients in all three models. The results demonstrate that the tumors in the present cohort overall grow at the rate of 0.04/month after nadir while on crizotinib, regardless of

their baseline tumor volume burden or clinical characteristics. The observation is similar to the results of prior studies of *EGFR*-mutant NSCLC patients, where their tumor growth rate was not affected by the baseline tumor volume or clinical variables including tumor stage at diagnosis and smoking status [25,26].

The limitations of the present study include a relatively small number of patients treated at a single institution studied retrospectively. Given the low frequency (2–7 %) of *ALK*-rearrangements in patients with NSCLC, a larger multicenter cohort will be necessary to validate the findings and additional cohorts will be needed to assess the newer generation of targeted agents. Serial tumor volume measurements were performed in one dominant lung lesion for each patient, and the other smaller lung lesions or extrapulmonary lesions were not included in the tumor growth rate assessments [26,28]. The prognostic value of tumor volumes of single dominant lesion has also been demonstrated in EGFR inhibitor-treated and ALK inhibitor-treated cohorts of advanced NSCLC patients [25–27]. Additionally, the approach using tumor volume growth rate is designed to be performed in parallel with RECIST-based assessment that practically captures systemic tumor burden in a standardized manner [1,18,25–27]. Future studies are planned to evaluate the tumor growth rate after nadir in patients treated with newer ALK inhibitors such as ceritinib and alectinib, to further understand the tumor volume kinetics of *ALK*-rearranged NSCLC.

In conclusion, the present study provided a reference value of tumor volume growth rate after nadir in *ALK*-rearranged NSCLC patients treated with crizotinib as their first ALK-directed therapy, which can be further studied and validated in larger cohorts of patients treated with crizotinib to define their slow tumor growth. The approach can also be applied in patients treated with newer ALK inhibitors, to further understand the tumoral behaviors and volume kinetics of *ALK*-rearranged NSCLC.

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